ORIGINAL ARTICLE

Meta-Analysis of Risk for Relapse to Substance Use After Transplantation of the Liver or Other Solid Organs

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For patients receiving liver or other organ transplants for diseases associated with substance use, risk for relapse posttransplantation is a prominent clinical concern. However, there is little consensus regarding either the prevalence or risk factors for relapse to alcohol or illicit drug use in these patients. Moreover, the evidence is inconsistent as to whether patients with pretransplantation substance use histories show poorer posttransplantation medical adherence. We conducted a meta-analysis of studies published between 1983 and 2005 to estimate relapse rates, rates of nonadherence to the medical regimen, and the association of potential risk factors with these rates. The analysis included 54 studies (50 liver, 3 kidney, and 1 heart). Average alcohol relapse rates (examined only in liver studies) were 5.6 cases per 100 patients per year (PPY) for relapse to any alcohol use and 2.5 cases per 100 PPY for relapse with heavy alcohol use. Illicit drug relapse averaged 3.7 cases per 100 PPY, with a significantly lower rate in liver vs. other recipients (1.9 vs. 6.1 cases). Average rates in other areas (tobacco use, immunosuppressant and clinic appointment nonadherence) were 2 to 10 cases per 100 PPY. Risk factors could be examined only for relapse to any alcohol use. Demographics and most pretransplantation characteristics showed little correlation with relapse. Poorer social support, family alcohol history, and pretransplantation abstinence of ≤6 months showed small but significant associations with relapse ($r = 0.17$-0.21). Future research should focus on improving the prediction of risk for substance use relapse, and on testing interventions to promote continued abstinence posttransplantation. *Liver Transpl 14:159-172, 2008.* © 2008 AASLD.

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Organ transplantation has become an increasingly accepted strategy for the treatment of end-stage diseases associated with substance abuse or dependence. For example, despite early reservations as to whether patients with alcoholic liver disease were appropriate transplant candidates,[1-4] alcoholic liver disease is now among the most common indications for liver transplantation in both the United States and Europe,[5-8] and short-term (1-5 yr) survival rates for these patients are similar to or exceed those of patients receiving transplantation for other types of liver disease.[5,9] A small literature suggests that favorable outcomes are also possible for liver and other solid organ transplant recipients with histories of other types of substance abuse (e.g., heroin use).[10-13]

Nevertheless, concerns remain regarding patients' risk of return to alcohol or other substance use posttransplantation, especially in light of a growing body of data showing that substance use relapse—especially return to

Abbreviations: PPY, persons (patients) per year; ES, effect size.

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heavy or "harmful" use[14]—bodes poorly for long-term graft function, extrahepatic health, and patient survival.[15-21] But how commonly do patients return to substance use after transplantation, and what are the strongest predictors of this outcome? Reviews and commentaries indicate that we cannot yet answer either part of this question. For example, crude rates (unadjusted for follow-up duration) of alcohol relapse after liver transplantation have been reported to range from 0 to 95%.[5,19,22-31]

Reviews summarizing alcohol relapse rates posttransplantation note that differences across studies are difficult to interpret or reconcile due to variations in study methodology, definition and assessment of relapse, and follow-up duration.[5,25,31,32] Addressing differences in follow-up duration has proved particularly vexing, with the most common approaches to date consisting of commenting on such differences qualitatively (without any corresponding empirical adjustment of rate estimates)[5,25,26,28,29] or considering small groups of studies piecemeal (e.g., examining the small group that report 6-month relapse rates, those reporting 12-month relapse rates, etc.).[22,23,32] Neither approach allows for full integration across studies. Moreover, despite the wide-spread promotion of strategies believed to reduce posttransplantation relapse risk (e.g., requiring that patients have >6 months of abstinence pretransplant or that patients participate in formal substance use rehabilitation programs),[31,33] reviews note that the empirical evidence linking such factors to posttransplantation relapse remains sparse and contradictory.[7,25,31,34,35] Finally, a long-standing debate has concerned whether patients with histories of substance use/abuse are at risk not only for relapse posttransplantation but for nonadherence to the medical regimen (either alone or in concert with substance use relapse).[3,36] Yet evidence to support or refute assertions of heightened nonadherence risk remains scattered across this literature[11,17,36-40] and has not received systematic review.

Without precise information about level of risk and predictors of risk for relapse to substance use after liver and other forms of organ transplantation, it becomes difficult either to: 1) appropriately target clinical resources to minimize the risk; or 2) design intervention research to empirically evaluate promising clinical strategies for risk reduction. Therefore, we performed a meta-analysis to achieve 2 goals. First, we sought to provide precise estimates of the rates of alcohol and illicit drug relapse in individuals receiving liver or other solid organ transplants. As part of this goal, we also examined posttransplantation rates of nonadherence to critical components of the medical regimen (e.g., taking immunosuppressant medications) in transplant recipients with pretransplantation histories of substance use. Where there was substantial variation in substance relapse or other nonadherence outcome rates across studies, we examined whether this variation could be explained by differences in study characteristics (e.g., study design). Second, we sought to determine whether substance use relapse was associated with features of pretransplantation substance use history and other psychosocial characteristics hypothesized to influence posttransplantation relapse risk.

MATERIALS AND METHODS

The methodology for conducting and reporting the meta-analysis followed established guidelines.[41,42]

Search Strategy and Study Selection

Eligible studies reported on transplant recipients with pretransplantation histories of substance abuse/dependence or diseases indicative of such use (e.g., alcoholic liver disease). Studies included in the present report were drawn from a larger literature search on nonadherence to the medical regimen (including substance use) after organ transplantation. We divided this literature into studies that focused on general transplant samples and studies that focused on samples of patients receiving transplantation due to substance use. The former samples were examined in an earlier meta-analysis.[43] In contrast, the present report examines all works describing samples of patients receiving transplantation due to substance use.

Figure 1 summarizes our study retrieval and selection strategy. From 691 articles initially retrieved, 603 articles were excluded from the analyses herein. As shown in Figure 1, articles were excluded if they provided no data on posttransplantation substance use relapse or any other nonadherence outcome in transplant recipients with substance abuse/dependence histories. Studies were also excluded if they provided neither: 1) the number of persons who relapsed (or had any other outcome we examined) and the duration of observation time for sample; nor 2) the association of relapse (or any other outcome) with at least 1 of the psychosocial risk factors we considered (as described below). Finally, studies were excluded if they reported on relapse or nonadherence exclusively in samples of patients with poor health outcomes (e.g., graft loss, death). The rationale for this exclusion was that studies limited to patients with poor outcomes, some of which can be produced by substance use, would not provide rate information generalizable to the larger group of transplant recipients who remained alive.

Data Extraction

Substance Use and Other Nonadherence Outcomes

Pairs of authors (1 of whom was author M.A.D.) reviewed all studies. The 3 primary outcomes for the present analyses pertained to substance use relapse: relapse to any alcohol use posttransplantation, relapse to heavy alcohol use, and relapse to any illicit drug use. Three secondary outcomes pertained to behaviors in other areas of the posttransplantation medical regimen: tobacco use, immunosuppressant medication nonadherence, and failure to attend clinic appointments. No other areas of nonadherence (e.g., failure to complete blood work and tests, failure to monitor vital signs) were examined in any report focused on transplant recipients with histories of substance use.

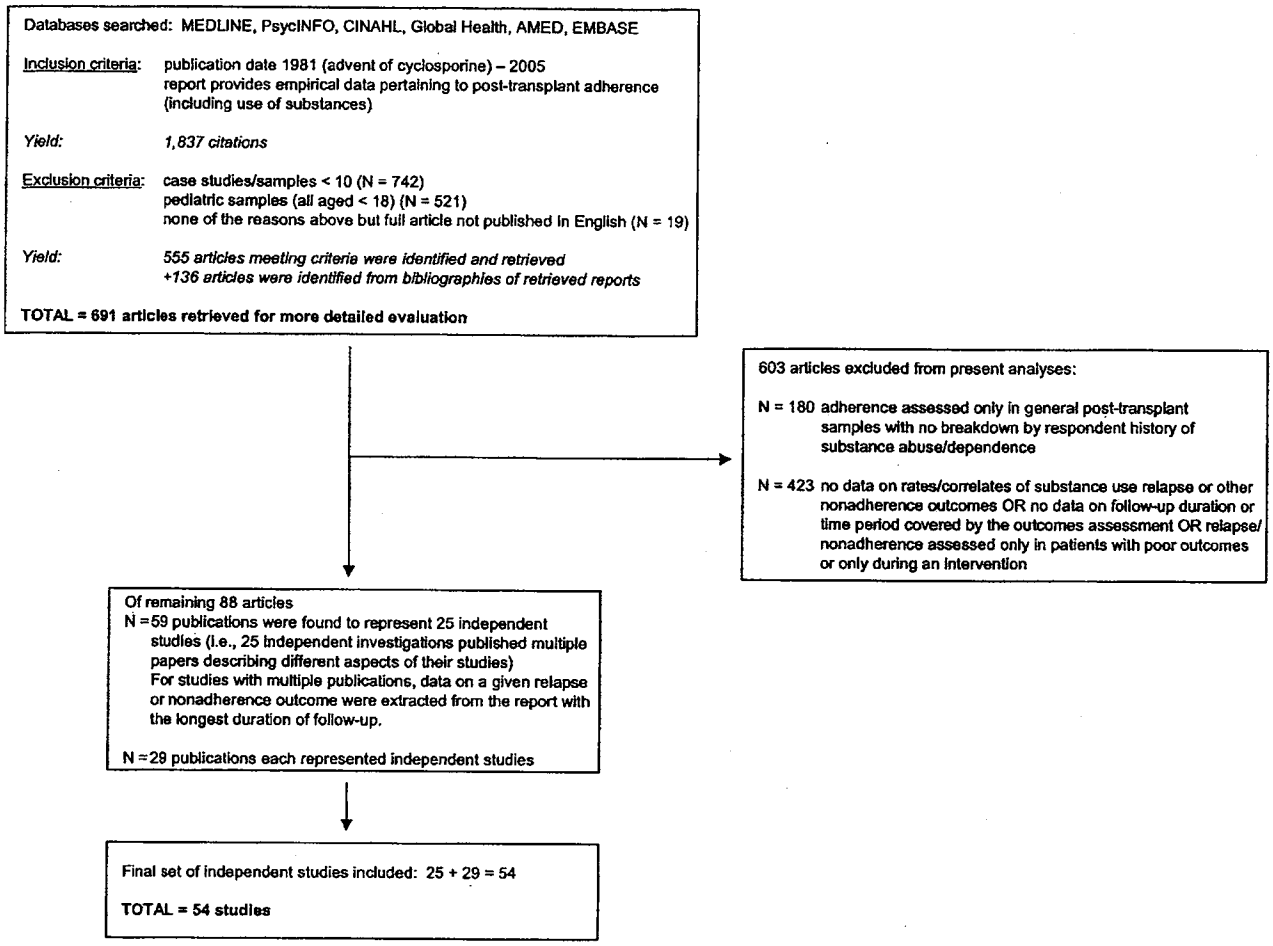


Figure 1. Identification of independent studies for current meta-analysis.

A total of 3 of our 6 outcomes—alcohol relapse, illicit drug relapse, and tobacco use—were consistently defined across the original study reports as any use (vs. none). For remaining outcomes (alcohol relapse with heavy use, nonadherence to immunosuppressants, and nonadherence to clinic appointments), we followed the standards of the Cochrane Collaboration[44,45] and other meta-analyses of nonadherence in nontransplant populations:[46] we extracted information from each study on the occurrence of each outcome based on the study authors' definition (i.e., their definition of what constituted heavy drinking, or their definition of nonadherence to immunosuppressants or required clinic appointments). (These definitions necessarily varied somewhat depending on the studies' method of outcome assessment; we evaluated the impact of method differences on outcome as described below.) Authors' definitions of medication and clinic appointment nonadherence reflected their transplant programs' requirements in these areas.

Assessment-Related and Other Study Characteristics

We aimed to categorize the method used to assess each substance use and nonadherence outcome into 5 broad groups:[46] 1) self-report (e.g., patient interview, paper-and-pencil survey, diary); 2) collateral report by family member or health care professional (e.g., through interview or survey); 3) biologic or other "indirect"[47] measure (e.g., blood level, electronic medication monitoring); 4) historical data retrieved from medical records; and 5) combinations of 2 or more of these methods (e.g., self report + medical record data). However, no studies were found that fell into categories (2) or (3). We also recorded descriptive information about each investigation (e.g., type of transplant studied, geographic region where the study was conducted, study design).

Finally, following current meta-analysis standards,[41] pairs of us rated each study on 5 components of methodologic quality, using a validated scoring system for each.[48] We employed a consensus approach in which any disagreements were resolved before assigning a final score. The 5 components (each rated as 1 = yes, 0 = no) were whether: 1) the sample was clearly described (e.g., including demographic information, dates of transplant); 2) the patients approached for enrollment were representative of the population of patients with histories of substance use who received transplantation at the study's site; 3) the sample enrolled was

representative of those approached; 4) the source of outcome data (e.g., on relapse or other areas of nonadherence) and the time period covered by the outcome measure were clearly described; and 5) analyses of outcome rates were appropriate (i.e., if patients varied in follow-up duration, rates were calculated via techniques such as survival analysis). A composite quality score was created for each study, which was the count of the number of these 5 areas that were rated as "yes" (total score range, 0-5).

Potential Correlates of Substance Use and Nonadherence Outcomes

From each study, we extracted information on the size of the associations of our outcomes with a series of psychosocial characteristics. We aimed to examine as many as possible of the characteristics hypothesized in the substance use and adherence literatures to be important.[15,23,25,26,31,32,34,43,46,49-52] However, there were only sufficient numbers of studies (i.e., ≥5 for any given psychosocial characteristic) for us to examine: 1) a single outcome, alcohol relapse (any use), in relation to 2) the variables of patient gender, age, education, marital status, employment status, social support, pretransplant psychiatric history (Axis I disorders), pretransplant illicit drug use, family history of alcohol abuse/dependence, duration of abstinence from substance use before transplantation, and participation in a substance use rehabilitation program before transplantation. (It is noteworthy that there were also too few studies to examine even the single outcome of alcohol relapse in relation to other outcomes such as immunosuppressant or clinic appointment nonadherence.) Among the potential psychosocial correlates of alcohol relapse, 1 variable, duration of pretransplant abstinence, has been used in some studies as a dichotomous variable (≤6 months of abstinence vs. longer abstinence), and in other studies as a continuous variable. Thus, we considered it both ways in the present analyses so that relevant information on abstinence duration from as many studies as possible could be evaluated. In addition, because it has been suggested that there is a strong negative association between time since transplantation and risk for alcohol relapse[5] (yet too few studies report any empirical estimate of this association), we examined the timing of relapse descriptively.

Statistical Analysis

Examination of Rates of Relapse and Nonadherence

Patients in most studies had unequal follow-up time, typically because they entered a given study at different time points (e.g., different transplantation dates) or were lost to follow-up at varying time points (e.g., due to death). Thus, given our goal to compare rates in the face of differences in duration of observation,[53,54] we examined event rates—e.g., cases of relapse—per 100 persons per year (PPY) (i.e., per 100 person-yrs of observation). If total person-yrs of observation was not reported directly, we calculated it from either reported cumulative probabilities or descriptive information about the distribution of follow-up duration in the sample.[53] The person-yrs metric is routinely used in examining health-related outcome rates in many patient populations.[55-58]

We calculated the pooled, or average, estimate of the rate in each study outcome (rate = cases per 100 PPY) across all contributing studies, as well as within each organ transplant type (when studies varied in the type of transplant recipients considered). The pooled estimate is a weighted average that takes within-study variance into account. It was calculated under a random effects model, to allow generalizability beyond the retrieved studies.[59] For each statistically significant pooled estimate, we evaluated the impact of publication bias (i.e., that studies finding outcome rates exceeding zero may have been more likely to be published) by calculating the "fail-safe N." This is the number of missing studies obtaining null findings that would need to be added to the analysis so that the pooled estimate would no longer be significant.[60,61]

For outcomes with substantial variability in rates among contributing studies (as determined with the Q test for heterogeneity), we used random effects meta-regression to determine whether the variability could be independently explained by any of 5 study characteristics: geographic location, year of publication, study design, study quality, and method of assessment of the study outcome.

Examination of Psychosocial Risk Factors in Relation to Study Outcomes

The association of alcohol relapse (any use) with each psychosocial variable was examined by extracting *r*, the Pearson correlation coefficient, as the measure of effect size (ES). (When the size of the association was not reported directly, we calculated it from the relevant test statistic reported for it, e.g., a *t*-test or a chi-squared value). The ES indicates the strength and irection of association between pairs of variables; we chose it for its flexibility and applicability across measurement scenarios (i.e., with continuous, dichotomous, or ranked variables[62,63]). For each statistically significant average ES, we calculated the fail-safe N. We determined whether there was significant variability in ES across studies with the Q test, and we examined whether study characteristics defined above accounted for the variability. Although we could not extract ES data on the association between time since transplantation and risk for alcohol relapse, we provide descriptive data relevant to this association.

RESULTS

Retrieved Studies

A total of 54 studies met our inclusion criteria; all but 4 pertained to liver transplant recipients. Table 1 provides descriptive information for the complete set of studies. (Appendix A lists each study and the substance use or other nonadherence outcomes examined; a bibliography is available from author M.A.D.) Similar numbers of studies were conducted in North America (all in

TABLE 1. Descriptive Information for 54 Independent Studies of Substance Use and Other Outcomes in Patients With Pretransplant Histories of Alcohol or Illicit Drug Use

Characteristic	Type of organ transplant			
	Total	Liver	Kidney	Heart
Number of studies	54	50	3	1
Year of earliest publication of any study examining outcomes	1983	1988	1983	1991
Study location, continent: % (n)				
North America	51.9 (28)	48.0 (24)	100.0 (3)	100.0 (1)
Europe	48.1 (26)	52.0 (26)	–	–
Total number of patients studied	3,651	3,551	53	47
Sample size: mean (SD)	68 (48)	71 (48)	18 (3)	47 (-)
Median	55	58	17	47
Range	11–209	11–209	15–21	–
Total person years of observation	13,821	13,414	111	296
Duration of observation or follow-up, yrs: mean (SD)	4.2 (2.7)	4.2 (2.7)	2.0 (0.6)	6.3 (-)
Median	3.5	3.4	2.0	6.3
Range	0.9–12.9	0.9–12.9	1.6–2.4	–
Study design, cross-sectional/retrospective (vs. prospective): % (n)	88.8 (48)	88.0 (44)	100.0 (3)	100.0 (1)
Study quality evaluation: % (n)				
Low (score 0–1)	3.7 (2)	2.0 (1)	33.3 (1)	–
Moderate (2–3)	50.0 (27)	48.0 (24)	66.7 (2)	100.0 (1)
High (4–5)	46.3 (27)	50.0 (25)	–	–
Outcomes examined: no. of studies				
Primary outcomes				
Alcohol relapse, any use	48	48	0	0
Alcohol relapse, heavy use	21	21	0	0
Illicit drug relapse, any use*	8	4	3	1
Secondary outcomes				
Tobacco use	3	3	0	0
Nonadherence to immunosuppressants	7	6	0	1
Nonadherence to clinic appointments	2	2	0	0

Abbreviation: SD, standard deviation.
*Includes 1 study of kidney recipients that reported on illicit drug use posttransplantation in patients with either alcohol or illicit drug use before transplantation. All remaining studies examining this outcome focused on return to illicit drug use in patients identified as having used illicit drugs before transplantation.

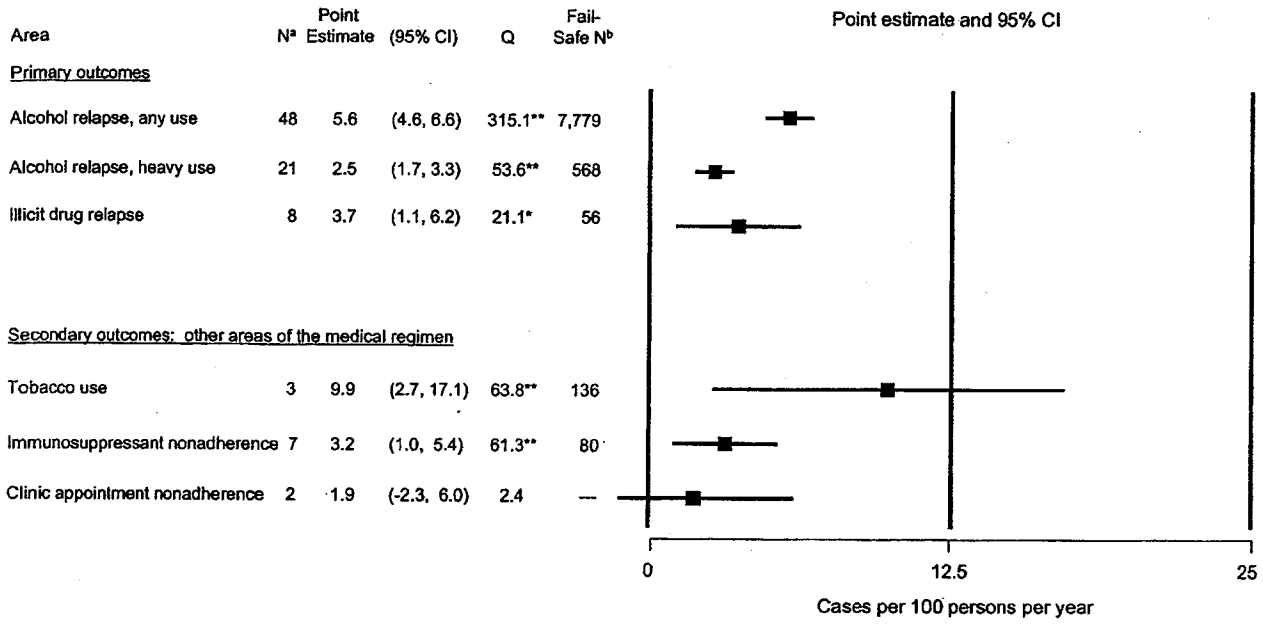
the United States) and Europe (including France, Germany, the United Kingdom, Spain, Austria, and Italy). Over 3,600 patients were included across all studies, contributing over 13,800 person-yrs of observation time. The average duration of observation was over 4 yrs, ranging up to almost 13 yrs. Most studies examined substance use or other nonadherence outcomes retrospectively, rather than by prospectively charting the incidence of the outcomes over time. The majority of the studies received total methodologic quality scores in the low to moderate range.

The number of reports contributing data on each of our primary and secondary outcomes are also shown in Table 1. Studies of posttransplantation alcohol relapse (any use) were most common and included only liver recipients. Although there are far fewer studies of illicit drug relapse, it has been considered across multiple types of organ recipients. The secondary outcomes have rarely been reported in individuals with pretransplantation histories of alcohol or illicit substance use.

Rates of Study Outcomes and Rate Differences by Type of Transplant

Figure 2 shows the average rate and 95% confidence interval for the primary and secondary outcomes. For example, the average rate for alcohol relapse (any use) was 5.6, or approximately 6 cases per 100 PPY of observation. The average rates for all outcomes except nonadherence to clinic appointments differ significantly from zero (i.e., confidence intervals do not include zero). The rate for tobacco use is higher than rates for any other outcomes, although its confidence interval is also wider than that of any other outcome.

The relatively large fail-safe Ns for the rates in Figure 2, especially for alcohol relapse (any use) and alcohol



[a]Number of studies examining each nonadherence outcome.

[b]Cannot be estimated for < 3 studies.

*p<.01 **p<.001

Figure 2. Pooled estimates of posttransplantation rates of substance use and other nonadherence outcomes. CI, confidence interval.

TABLE 2. Rates of Study Outcomes by Type of Organ Transplant (Cases Per 100 person per year)[a]

	Type of organ transplant						
	All Types	Liver		Kidney		Heart	
Outcome area	Rate (SE)	Rate (SE)	N[b]	Rate (SE)	N[b]	Rate (SE)	N[b]
Illicit drug recidivism*	3.7 (1.3)	1.9 (1.4)	4	5.9 (2.6)	3	6.4 (2.6)	1
Nonadherence to immunosuppressant medications	3.2 (1.1)	2.6 (1.1)	6	—	0	6.1 (2.7)[c]	1

[a]All other outcomes were examined exclusively in liver recipients.
[b]Number of studies of each transplant type that examined each area of nonadherence.
[c]A comparison with liver recipient studies could not be performed due to the small sample size in this group.
*Significant differences ($P < .05$) in rates of nonadherence were found between studies of liver recipients vs. the combined group of studies of kidney and heart recipients, based on meta-ANOVA.

relapse with heavy use, indicate that these average rates are very robust to the discovery of many additional studies reporting null findings (i.e., the observed rates are not artifacts of publication bias favoring reports finding large, significant rates). The Q tests in Figure 2 indicate that, except for clinic appointment attendance, there is significant variability in the rates across studies. Is this variability explained by type of transplant (i.e., liver vs. kidney or heart)? Only 2 outcome areas have been examined across multiple types of transplant recipients: as shown in Table 2, the rate of illicit drug relapse was significantly lower in liver transplant recipient studies than in studies of other types of recipients. The rate of immunosuppressant nonadherence appeared to be lower in liver transplant recipients than in heart transplant recipients. However, we could not formally test this difference because the heart transplant recipient rate was based on a single study.

Study-Related Characteristics Accounting for Variability in Outcome Rates

We focused on the outcomes where there was significant variability and, because meaningful analysis is difficult with small numbers of studies, we considered only those outcomes with more than 5 contributing studies. Results

TABLE 3. Study Characteristics Potentially Accounting for Variability in Outcome Rates (Per 100 PPY) Across Independent Studies of Patients with Pretransplantation Histories of Alcohol or Illicit Drug Use[a]

	Outcome Domain															
	Alcohol Relapse, any use				Alcohol Relapse, heavy use				Illicit Drug Relapse				Nonadherence to Immunosuppressant Medications			
Study Characteristic	rate	(SE)	N[b]	Z	rate	(SE)	N[b]	Z	rate	(SE)	N[b]	Z	rate	(SE)	N[b]	Z
Study location																
North America	4.4	(0.7)	22	3.53**	1.2	(0.5)	7	3.35**	3.7	(1.3)	8	—	5.0	(1.5)	4	2.60**
Europe	6.7	(0.7)	26		3.2	(0.4)	14		—				1.4	(1.4)	3	
Year of publication																
1983–1995	6.7	(0.8)	17	4.63***	2.4	(0.6)	8	0.90	6.4	(2.0)	3	0.35	4.9	(1.5)	4	1.38
1996–2005	5.1	(0.6)	31		2.6	(0.5)	13		2.2	(1.3)	5		1.6	(1.5)	3	
Study design																
Cross-sectional/ retrospective	5.5	(0.5)	42	0.11	2.6	(0.4)	19	—	3.7	(1.3)	8	—	3.7	(1.3)	6	—
Prospective	6.8	(1.6)	6		2.2	(1.2)	2[d]		—				1.7	(3.0)	1[d]	
Study quality																
Low/moderate (0-4)[c]	5.4	(0.7)	25	0.13	2.5	(0.7)	8	1.54	5.1	(1.5)	6	—	4.5	(1.8)	2[d]	—
High (5–6)	5.9	(0.7)	23		2.6	(0.5)	13		1.5	(1.8)	2[d]		2.5	(1.2)	5	
Method of assessment[d]																
Medical record	4.6	(0.6)	30	(ref)	3.1	(0.7)	9	(ref)	4.5	(1.5)	6	—	2.4	(1.5)	4	1.30
Self-report	8.6	(1.7)	5	3.53**	1.9	(0.9)	4	1.43	50.0	(50.0)	1[d]		7.8	(2.7)	2[e]	
Multiple sources	7.2	(1.0)	13	3.56**	2.4	(0.6)	8	0.47	0.8	(3.0)	1[d]		1.7	(2.9)	1[e]	

[a]The meta-regression results in this table also controlled for differences in type of transplant (when studies of more than one type were available) in examining effects of study characteristics on rates of the outcomes.
[b]Number of studies included in each category of a given study characteristic, e.g., there were 17 studies of alcohol use published between 1983–1995.
[c]This category combined studies of low and moderate quality because there were too few low quality studies to be examined separately.
[d]There were too few studies in this category to be examined in the analyses.
[e]The studies in these categories were combined and then compared to medical record assessment methodology because there were too few studies in each category to allow for separate comparisons.
*$P < .05$. **$P < .01$. ***$P < .001$.

for the 4 outcomes meeting these criteria are shown in Table 3. For each outcome, the estimated rate is shown according to study characteristic. For example, for relapse to any alcohol use, the second column of Table 3 shows that European studies had a higher average rate (6.7; ~7 cases per 100 PPY) than North American studies (rate of 4.4). This difference in rates was statistically significant ($Z = 3.53$; $P < 0.01$). European studies also yielded significantly higher rates of relapse to heavy alcohol use. However, European studies showed lower rates of immunosuppressant nonadherence.

Table 3 shows that 2 other study characteristics were associated with significantly greater risk for relapse to any alcohol use: study publication in 1995 or earlier, and use of either self-report or multiple method approaches to assessment. No study characteristic other than geographic location was associated with any other outcome.

Associations of Outcomes With Psychosocial Variables

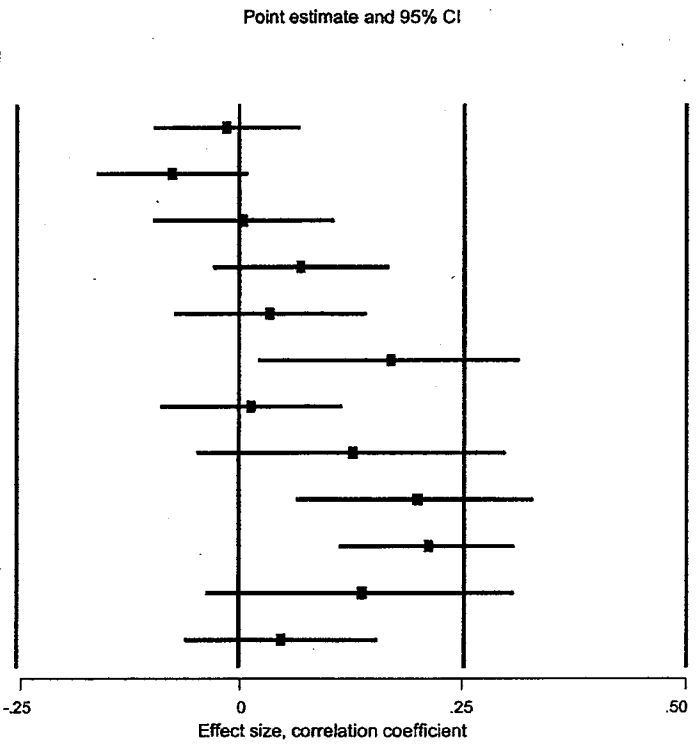
We were able to examine alcohol relapse (any use) in relation to 12 potential psychosocial risk factors. (As noted earlier, no other outcome was examined in sufficient numbers of studies in relation to any risk factors.) Figure 3 shows the direction and strength of the alcohol relapse-psychosocial variable correlations, as well as the number of studies examining each correlation. For example, across the 14 reports contributing data on the alcohol-gender correlation, the average ES was $r = -0.01$ (confidence interval, −0.10-0.07). Only 3 of the 12 psychosocial variables were significantly correlated with alcohol relapse: poorer social support, a family history of alcohol abuse/dependence, and duration of pretransplantation abstinence of ≤ 6 months (ESs of 0.17, 0.17, and 0.21, respectively; confidence intervals not overlapping with 0). The fail-safe Ns of 9 or less for social support and family history are small, but the fail-safe N of 179 for abstinence ≤ 6 months suggest that this latter association with alcohol relapse is robust to the discovery of many additional reports with null effects.

Q was significant for several ESs in Figure 3. However, no study characteristics (e.g., design, quality) significantly accounted for the observed variability in ESs across studies.

Finally, although we could not quantitatively exam-

Correlate	N of Studies	Average ES r (95% CI)	Q	Fail-Safe N
Male gender	14	-.01 (-.10, .07)	18.6	—
Older age	12	-.08 (-.16, .01)	14.6	—
Greater education	5	.01 (-.09, .11)	1.1	—
Unmarried	8	.07 (-.03, .17)	5.8	—
Unemployed before transplant	5	.04 (-.07, .14)	1.2	—
Poorer social support	6	.17 (.02, .31)	9.1	9
Pre-transplant psychiatric history	7	.02 (-.09, .12)	2.2	—
Pre-transplant illicit drug use	8	.13 (-.05, .30)	24.5*	—
Family history of alcohol abuse/dep.	6	.20 (.06, .33)	8.2	16
Pre-tx alcohol abstinence ≤ 6 mos.	17	.21 (.11, .31)	41.2*	179
Shorter pre-tx alcohol abstinence	9	.14 (-.04, .31)	27.3**	—
No pre-tx alcohol rehab. program	9	.05 (-.06, .16)	12.2	—

*p < .01 **p < .001



*Positive effect sizes indicate associations of alcohol recidivism with male gender, greater age, greater education, unmarried status, pre-transplant unemployment, poorer social support, pre-transplant history of psychiatric disorder, pre-transplant history of illicit drug use, family history of alcohol abuse/dependence, pre-transplant alcohol abstinence ≤ 6 mos, shorter pre-transplant abstinence time, and lack of pre-transplant participation in an alcohol rehabilitation program.

Abbreviations: ES, effect size; CI, confidence interval; tx, transplant; dep, dependence; rehab, rehabilitation

Figure 3. Associations between posttransplantation alcohol relapse (any use) and psychosocial variables.

ine an association between time since transplantation and alcohol relapse risk (because too few studies reported a relevant ES), Figure 4 shows descriptive data on relapse timing. A total of 11 studies reported the earliest and latest time posttransplantation at which relapse occurred (and sometimes reported the midpoint), based on survival analysis. Figure 4 shows that risk for alcohol relapse (any use) begins early posttransplantation and may continue for many years. Of the 9 studies following patients beyond 7 yrs, 6 observed new cases of relapse to continue to occur as late as 4 to 9.5 yrs posttransplantation. Some of the 11 studies show a long time lag between the final occurrence of relapse and continued follow-up in the remainder of the sample who remained abstinent (as denoted by the dashed lines that continue to the end of follow-up in Fig. 4). Others show that new cases of relapse continued to occur through much or all of the follow-up period.

DISCUSSION

The literature on posttransplantation relapse to substance use consists almost exclusively of studies of liver transplant recipients. With few exceptions, then, the interpretation of our findings is limited to these patients. With this caveat, the rates of the outcomes we examined, summarized in Figure 2, provide essential information to guide clinicians' assessments of the overall risk of these outcomes in their patients. Such rate estimates can also be valuable for developing clinical strategies to reduce or limit risk.[43,53] From a research standpoint, Figure 2 reveals the areas for which there remains limited posttransplantation risk information in patients with substance use histories. Alcohol relapse has clearly received the greatest attention to date, despite equally salient concerns about relapse risk in the growing numbers of transplant recipients with other types of substance use histories.[23,64,65] In particular, many patients with hepatitis C virus—now the most common indication for liver transplantation, alone or in combination with alcoholic liver disease[5,6]—are likely to have acquired the virus via illicit drug use.[23] Thus, relapse to drug use demands increased scrutiny in future studies.

The average rates of all outcomes we examined suggest that during any given year of observation, most transplant recipients with substance use histories will neither use substances nor become nonadherent to components of the medical regimen. For example, the posttransplantation healthcare provider can expect to see only approximately 6 patients relapse to alcohol use and 4 relapse to illicit drug use for every 100 former substance users during a given year of follow-up. Tobacco use posttransplantation was the most prevalent outcome, at approximately

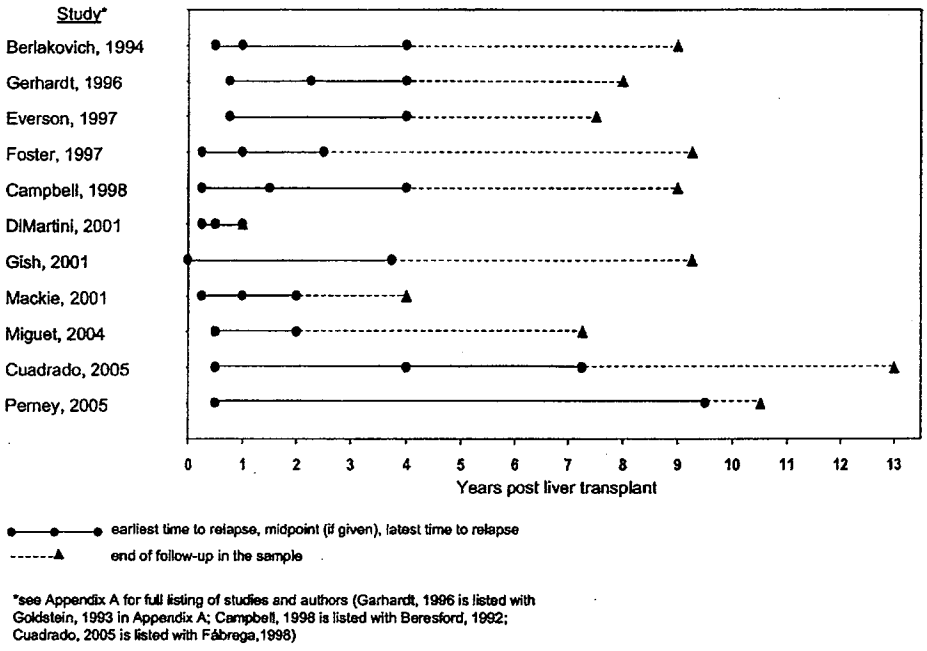


Figure 4. Time to alcohol relapse (any use) after liver transplantation. For each of 11 studies reporting time to relapse after adjusting for differences in patients' follow-up duration, the range of time to relapse is plotted (earliest point, midpoint [mean or median], latest point), as well as length of total follow-up in the sample.

10 cases per 100 PPY. Although this estimate was based on only 3 studies, our finding of a relatively high prevalence of tobacco use is consistent with the increased attention that this outcome is receiving in the clinical literature,[66-69] including mounting evidence that it is associated with significant morbidities (e.g., lung and oropharyngeal cancers;[70] vascular complications[69]) after liver transplantation. The tobacco use rate found in the present analysis was greater than the rate of 3.4 cases per 100 PPY that we observed in our earlier meta-analysis of general transplant samples.[43] Overall, our findings support the need for smoking cessation programs to be more widely available to transplant patients,[68] particularly those with substance use histories because these individuals are more likely than other patients to also be smokers.[66]

In contrast, we observed a lower rate of immunosuppressant medication nonadherence than we found in our earlier analysis of general liver transplant samples (3.2 cases vs. 6.7 cases per 100 PPY, respectively). These results, then, belie assertions that persons with pretransplantation substance use histories are at greater risk for medication nonadherence than other patients. We could not examine, however, whether relapse to substance use posttransplantation elevates the risk for medication nonadherence because too few studies have considered this issue.

With respect to our primary outcomes, relapse to any alcohol use after liver transplantation was over twice as common as relapse with heavy alcohol use (almost 6 vs. less than 3 cases per 100 PPY). This suggests that only a minority of recipients who return to alcohol use may become heavy or "harmful" drinkers. (It can be argued that relapse to "any" alcohol use does not specify quantity of use and that perhaps most if not all individuals in the 49 studies reporting on "any use" actually relapsed to heavy use. However, 20 of the 49 studies reported both outcomes for their cohorts (see Appendix A). The findings from these 20 studies are virtually identical to those reported across all available studies: approximately 6 cases per 100 PPY return to any use, while less than 3 per 100 PPY return to heavy use.)

The alcohol use outcome rates are annualized rates. Since our descriptive analysis of time to onset of drinking (Fig. 4) suggested that new cases are observed from early posttransplantation to many years later, it is the *cumulative* rates of relapse to any use or heavy use that become particularly worrisome. For example, at a rate of almost 6 cases of relapse to any alcohol use per 100 patients per year (PPY), the cumulative incidence rate would be approximately 11 cases by 2 yr posttransplantation, 28 cases by 5 yr, and so on. In Figure 5, we plot the expected cumulative incidence rate for both of the alcohol outcomes, based on the meta-analysis findings. Figure 5 also shows the rates extracted from the individual studies. It is possible that the cumulative incidence rates would eventually level off, but our analyses do not allow us to determine when that might occur. However, the fact that some studies report new cases of relapse even many years posttransplantation suggests that cumulative rates may continue to grow even in the late-term years. As shown in Figure 5, very few studies have followed cohorts beyond 7 to 8 yrs posttransplantation, and thus it is difficult to extrapolate beyond that point.

Our results suggest that illicit drug relapse was slightly less common than relapse to any alcohol use. It is the only outcome that was considered in multiple studies beyond liver transplantation. Indeed, the rate of illicit drug relapse was significantly higher in recipients of other organs than in liver recipients. We suspect that this partly reflects the fact that most studies of other types of recipients were conducted earlier than the liver

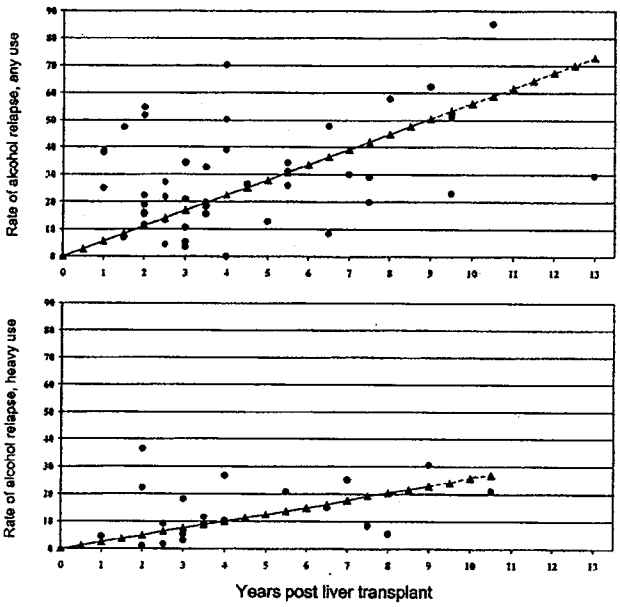


Figure 5. Rate of alcohol relapse as a function of time since transplantation. Solid line shows estimate from meta-analysis (alcohol relapse, any use: 5.6% increment annually, i.e., 5.6 cases per 100 PPY; alcohol relapse, heavy use: 2.5% increment annually). This line becomes dashed after 9 years due to the limited number of studies available. Points show individual studies' rates. Individual studies' rates were calculated at the end of follow-up for studies that followed all patients for the same duration or for studies that adjusted for differences in follow-up duration through survival analysis; otherwise, studies' rates represent the midpoint of each study's follow-up period.

recipient studies. These kidney and heart recipient reports either note that pretransplantation abstinence was not as closely monitored as is current practice,[11] do not comment on whether there was any monitoring,[10,71] or emphasize issues other than abstinence (e.g., adherence to dialysis for kidney patients) were more important both pre- and posttransplantation for these patients.[10,72]

Geographic and other study methodologic characteristics were related to variations in the substance use and nonadherence outcome rates. Of particular note, European studies showed higher rates of relapse to any alcohol use and relapse with heavy alcohol use, compared to North American (United States) studies. We know of no evidence to suggest that the higher European rates reflect any differential degree of emphasis across transplant programs on the importance of abstinence either before or after transplantation. Instead, the effects may arise from the fact that alcoholic liver disease patients in Europe are exposed to cultures with higher average levels of alcohol consumption than in North America.[73] These environmental conditions may make it more difficult for liver transplant recipients with histories of alcohol use to continue to abstain from alcohol posttransplantation.

Independent of geographic location, studies published after 1995 have found lower rates of relapse to any alcohol use. This may reflect transplant programs' increasingly stringent protocols for the selection of liver transplant candidates with histories of alcohol use.[15,16,26,33] Finally, assessment method affected observed alcohol relapse rates. Self-report alone and multiple-method assessments (typically self-report + biological measures such as blood tests, or self-report + collateral report) yielded the highest rates of alcohol relapse. Our findings indicate that medical record reviews alone seriously underestimate alcohol relapse rates.

An important objective of our analysis was to determine the degree to which study outcomes were associated with patient psychosocial characteristics. The literature permitted us to examine only 1 outcome, relapse to any alcohol use, in relation to only some hypothesized psychosocial predictors. We found that patient demographic characteristics, pretransplantation psychiatric and illicit drug history, and pretransplantation participation in rehabilitation bore little to no association with relapse. A total of 3 significant associations were found, although they were modest in size: poorer social support, a family history of alcohol abuse/dependence, and a pretransplantation duration of abstinence of 6 months or less each mildly increased the risk for posttransplantation relapse (correlations of 0.17 to 0.21). Overall, the fact that these modest associations were statistically reliable indicates that these variables have some predictive utility. However, they are not strong enough to predict risk with a high degree of accuracy. In the case of pretransplantation abstinence, its limited impact may be due to the fact that transplant programs strive to apply the "6-month rule" as a key criterion for candidate selection. If the highest risk patients (those with shorter or no abstinence) are largely eliminated from the candidate pool, then it would be expected that this variable should show only a limited correlation with relapse.

There are limitations to the present meta-analysis. We included only studies in which the full text was in English. However, the number of potentially relevant non-English reports was minute relative to the number of reports reviewed for possible inclusion. We have already noted other limitations that reflect the areas of focus and omission within the body of research that we synthesized: 1) little consideration of samples beyond liver transplantation; 2) beyond substance use outcomes, consideration of nonadherence in only a narrow range of the components of the medical regimen; 3) examination of psychosocial variables only in relation to relapse to any alcohol use, despite calls for the literature to focus on heavy or harmful use[7,8,14]; 4) inability to examine associations between posttransplantation substance use relapse and medical regimen adherence because too few studies examined such effects; and 5) inability to examine many variables proposed to be important predictors of substance use relapse (e.g., whether past substance use met criteria for dependence vs. abuse, presence of personality disorder) because too few studies have included them. Indeed, these areas of focus and omission in the literature provide a roadmap for work in the future.

Several additional challenges must also be addressed in new research, given our findings. First, in terms of

prediction of relapse risk, it may be most important to determine *how many* risk factors a person possesses, even if each of those risk factors alone bears only a weak association with relapse. The idea that a constellation of risk factors may be critical is not new.[36,74,75] But research to date typically evaluates the independent effect of each factor rather than searching for additive predictive power and attempting to identify a critical threshold of risk burden. The modest findings from the present analyses—that no single factor seems to be of major importance as a predictor—suggests that a new approach is needed. Alternatively, our findings may indicate that careful candidate selection has eliminated the highest risk patients—but the fact that cumulative risk for relapse appears ultimately rather large suggests that there is still room for improving prediction.

Second, research to develop and test posttransplantation abstinence-promoting interventions is essential. Such work need not await the identification of risk factors if a model of "universal prevention"[76] is adopted, in which preventive interventions are offered to *all* recipients with pretransplantation histories of substance use. Posttransplantation intervention research in this area is undoubtedly difficult, given patients' medical burden, complex treatment regimen, and frequent denial of need for intervention.[77] Yet, given our findings regarding enduring risk for substance use relapse after transplantation, intervention efforts would be well-justified.

APPENDIX A

TABLE A1. Independent Studies Included in Meta-Analysis

Study first author, year (first author, year of additional related publications)	Country	Outcome areas examined: Alcohol relapse, any use	Alcohol relapse, heavy use	Illicit drug relapse, any use	Tobacco use	Nonadherence to immunosuppressant medications	Nonadherence to clinic appointment follow-up	Examined psychosocial correlates included in the meta-analysis
Liver transplant studies								
Starzl, 1988	USA	X						
Kumar, 1989 (Arria, 1991)	USA	X	X					X
Bird, 1990	UK	X						
Beresford, 1992 (Lucey, 1992, 1994, 1997; Beresford, 1994; Campbell, 1997, 1998)	USA	X	X			X		X
Doffoel, 1992	France	X						
Knechtle, 1992	USA	X	X					
Bonet, 1993 (Van Thiel, 1995; Tringali, 1996)	USA	X				X		X
Gish, 1993	USA	X						X
Goldstein, 1993 (Tripp, 1996; Gerhardt, 1996)	USA	X	X					X
Osorio, 1993 (Osorio, 1994)	USA	X						X
Pageaux, 1993 (Pageaux, 1999; 2003)	France	X	X		X			X
Berlakovich, 1994a (Berlakovich, 1994b, 1999)	Austria	X	X					X
Howard, 1994 (Pereira, 1997; 2000)	UK	X	X			X	X	X
Krom, 1994 (Jauhar, 2004)	USA	X						X
Poynard, 1994 (Poynard, 1999)	France	X						

TABLE A1. (Continued)

Study first author, year (first author, year of additional related publications)	Country	Outcome areas examined: Alcohol relapse, any use	Alcohol relapse, heavy use	Illicit drug relapse, any use	Tobacco use	Nonadherence to immunosuppressant medications	Nonadherence to clinic appointment follow-up	Examined psychosocial correlates included in the meta-analysis
Raakow, 1995 (Rommelspacher, 1996)	Germany	X	X					
Reeck, 1995	Germany	X						
Durand, 1996	France	X	X					
Zibari, 1996	USA	X						
Anand, 1997 (Tang, 1998)	UK	X	X					X
Chapman, 1997	USA	X						
Coffman, 1997	USA	X		X				X
Everson, 1997 (Talamantes, 1998)	USA	X	X			X		
Foster, 1997	USA	X		X				X
Pera, 1997	Spain	X						
Stephanini, 1997	Italy	X	X					
Wiesner, 1997	USA	X						
Fábrega, 1998 (Cuadrado, 2005)	Spain	X			X	X		X
Heineman, 1998	Germany	X						
Berlakovich, 1999a (Berlakovich, 1999b; 2000)	Austria	X				X	X	
Conjeevaram, 1999	USA		X					
Gledhill, 1999	UK	X	X					
Newton, 1999	USA	X		X				
Romano, 1999 (Rodriguez Romano, 2002)	Spain	X						
Talaulicar, 1999	Germany	X						
Burra, 2000 (Burra, 2001)	Italy	X	X					X
DiMartini, 2000	USA	X						
Jain, 2000 (Bellamy, 2001)	USA	X						X
Platz, 2000	Germany	X						X
DiMartini, 2001 (DiMartini, 2005)	USA	X			X			X
Gish, 2001	USA	X						X
Karman, 2001	USA	X	X					
Mackie, 2001	UK	X	X					X
Ayata, 2002 (Goldar-Najafi, 2002)	USA	X						
Tome, 2002 (Varo, 2002)	Spain	X	X					
Walter, 2002	Germany	X						X
Liu, 2003	USA			X				
Miguet, 2004	France	X	X					X
Bjornsson, 2005	Sweden	X	X					X
Perney, 2005	France	X	X					X
Kidney transplant studies								
Stevens, 1983	USA			X				
Gordon, 1986	USA			X				
Butkus, 2001	USA			X				
Heart transplant studies								
Hanrahan, 1991 (Hanrahan, 2001)	USA			X		X		

NOTE: Each row in this table describes an independent study of a given type of transplant recipient. A bibliography of the studies is available from author M.A.D.

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March 21, 2006

Dollene Tyler
First Health PPO
Phone 800 774 4506 prompt 1 Ext 8334
FAX: 281 986 8210

Ralph Neal
MR #1937497 DOB 9/4/1946
SS# 383467250 Policy#8593548

Dear Ms. Tyler:

This letter is to request prior authorization for combined liver and kidney transplantation on Mr. Ralph Neal. I will briefly outline his history as well as the reason for this request.

Mr. Neal is a 59 year old with presumed alcoholic cirrhosis who initially presented with recurrent ascites, shortness of breath and leukocytosis through an outside hospital. He was found to be with ascites and acute and chronic renal failure as well as pulmonary edema and pleural effusion. He was transferred to the University of Wisconsin Hospital and Clinics in Madison, Wisconsin on Monday, March 10, 2006 for further evaluation and treatment. At the time of his transfer he required intensive care unit stay for initiation of CVVH. The patient had failed to respond to fluid bolus and the diagnosis of hepatorenal syndrome on top of chronic kidney disease was considered. A transplant consult was also initiated at the point in time. Mr. Neal was discovered to have cirrhosis when he underwent Whipple procedure approximately one year ago. He is has intermittently continued to consume alcohol since that diagnosis with his last alcohol consumption approximately six weeks prior to this admission.

Past medical history reveals cirrhosis presumably secondary to alcohol abuse; status post Whipple procedure in March of 2005 for history of pancreatic mass that turned out to be benign. The patient has a history of esophageal dilatation, fracture of his left humerus, foot drop of his right foot after the Whipple procedure was performed, however, this has now resolved. He also had a cholecystectomy at the time of his Whipple procedure.

He does not have any known allergies. He is on multiple medications including acetylcysteine, Tums, adromycine, ferrous sulfate, folic acid, Lactulose, midodrine, multivitamin, vitamin K, ranitidine, thiamine, vitamin B, acyclovir, calcium carbonate, Mycelex troche, darbopoetin, flagyl, piperacillin and prednisone.

Family history reveals that his father died of an unknown cause. His mother died at the age of 83 from old age. He has one sister who has had a stroke and one sister who is alive and well.

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Social history reveals that he married and he lives with his wife. He has consumed 2-3 alcohol beverages daily for approximately 30 years. He denies any tobacco use or intravenous drug use.

Physical exam reveals his temperature 36.2, heart rate 92, respiratory rate 14, and blood pressure 110/58 with an oxygen saturation of 100% on room air. His weight is 75kg. He is a thin, frail looking icteric male resting comfortably. He is conversant and pleasant. His pupils are equal, round and reactive to light. Scleras are icteric. He does not have any oral lesions, oral mucosal is moist. He has no lymphadenopathy noted in his neck. His chest is clear on auscultation although breath sounds in the bases. He has a normal S1 and S2 with no murmurs, gallops or rubs with his heart. His abdomen is round with hypoactive bowel sounds. His radial and pedal pulses are present bilaterally. He is alert and oriented x 3. His speech is clear and appropriate. He follows commands and moves all extremities. He has been transferred out of the ICU and is currently on the liver failure floor. He continues on hemodialysis intermittently.

I have attached a copy of his multiple tests along with his laboratory reports that are most up-to-date. He has had an echocardiogram as well as a heart stress test that I have also enclosed for your review. You can see that with his INR of 3.0, bilirubin of 5 and creatinine of 2.8, he has a MELD score of 39.

In summary we are requesting coverage for combined kidney and liver transplantation for Mr. Ralph Neal. Although Mr. Neal has only been able to demonstrate six weeks of total abstinence prior to this hospitalization, we feel that he is sincere in his willingness to seek out treatment programs in his local area. Although our normal abstinence period is six months we do not feel that is overall health will allow us to wait that total six month period. We feel that he does have a supportive family in place as well to help him through this recovery process. Right now we see no technical, medical, infectious or psychosocial contraindications to proceeding and feel that we should place his name to the active liver transplant waiting list. If you have any further questions or concerns after review of this request do not hesitate to contact me in the Transplant Program at 608 263 2260. I look forward to your timely reply.

Sincerely,

Anthony D'Alessandro M.D.
Professor of Surgery
Division of Transplantation

Dictated by Mary Douglas RN MSN
Clinical Transplant Coordinator

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